UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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| WASHINGTON LEGAL FOUNDATION,<br><br>Plaintiff,<br><br>v.<br><br>MICHAEL A. FRIEDMAN, M.D., in his official capacity as Acting Commissioner, Food and Drug Administration and,<br><br>DONNA SHALALA, in her official capacity as Secretary, Department of Health and Human Services<br><br>Defendants. | ) | Civil Action No. 94-1306 (RCL) |

MEMORANDUM OPINION

This matter comes before the court on the parties' cross-motions for summary judgment. Upon consideration of the memoranda filed in support of and in opposition to the respective motions, the relevant legal authorities, and the entire record, and finding that there is no genuine issue of material fact, plaintiff's motion for summary judgment will be granted and defendants' cross-motion will be denied.

I. FACTUAL BACKGROUND

Plaintiff Washington Legal Foundation ("WLF") is a non-profit public interest law and policy center that defends "the rights of individuals and businesses to go about their affairs

without undue influence from government regulators." See Complaint ¶ 5. In this action, WLF seeks to enjoin the Food and Drug Administration, ("FDA") and the Department of Health and Human Services ("HHS") from enforcing policies restricting certain forms of manufacturer promotion of off-label uses for FDA-approved drugs and devices. The policies at issue -- expressed through Guidance Documents -- concern manufacturer distribution of reprints of medical textbooks and peer-reviewed journal articles ("enduring materials"), and manufacturer involvement in continuing medical education seminars and symposia ("CME"). See Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074 (1997); Advertising and Promotion; Guidances, 61 Fed. Reg. 52800 (1996).

Plaintiff seeks a declaratory judgment that the FDA policies expressed in the Guidance Documents violate the rights of its members under the First Amendment of the Constitution. It further requests that the court enter preliminary and permanent injunctions against defendants, preventing them from enforcing, relying upon, or otherwise giving effect to the Guidance Documents.

A. Statutory & Regulatory Framework

The FDA derives its authority to regulate various aspects of the medical and pharmaceutical industries from a complex statutory and regulatory scheme, a major portion of which is

embodied in the Food, Drug and Cosmetic Act, 21 U.S.C. § 301, et seq. In order for a prescription drug or class III medical device[1] to be distributed by a manufacturer in interstate commerce, the manufacturer is required to demonstrate, through a rigorous series of pre-clinical and clinical trials, that the drug or medical device is both safe and effective for each of its intended uses. 21 U.S.C. § 355(a),(b),(j). FDA makes its final approval decisions under the "substantial evidence" standard. See 21 U.S.C. § 355(d).

As part of the approval process, the FDA also reviews the proposed "labeling" for the drug, which includes, inter alia, all proposed claims about the drug's risks and benefits, as well as adequate directions for use. See, e.g., 21 U.S.C. § 352(f). Labeling is a term of art that encompasses all written, printed or graphic material "(1) upon any [drug or device] or any of its containers or wrappers, or (2) accompanying such [drug or device]." 21 U.S.C. § 321(k) & (m). The most self-evident form of labeling is the package insert that accompanies the drug, but the term has also been construed to include nearly every form of drug company promotional activity, including booklets, pamphlets, mailing pieces, bulletins, and all literature that supplements,

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[1]For the most part, the distinctions between prescription drugs and medical devices are not relevant to the First Amendment issues addressed here. In order to avoid unnecessary repetition, the term "drugs" should be understood to encompass both prescription drugs and medical devices.

explains, or is otherwise textually related to the product. See 21 C.F.R. § 202.1(1)(2) (1997); Kordel v. United States, 335 U.S. 345, 350 (1948); United States v. Vitamin Indus., Inc., 130 F. Supp. 755, 765-66 (D. Neb. 1955). The FDA will only approve the new drug application if the labeling conforms with the uses that the FDA has approved.

Congress has closely examined whether alternative uses for approved drugs -- treatments not on the approved label -- should be subjected to the same FDA review procedures as the initial claim. In 1962, Congress amended the definition of a "new drug," 21 U.S.C. § 321(p), to make clear that drugs must be demonstrated safe and effective for "use under the conditions prescribed," meaning that all uses for a drug must obtain FDA approval. See also 108 Cong. Rec. S17366 (daily ed. Aug. 23, 1962) (statement of Senator Eastland). Therefore, if a manufacturer wishes to market or promote a product for an unlabeled use, it must resubmit the drug for another series of clinical trials similar to those from the initial approval. Until this subsequent approval has been granted, the unapproved use is considered to be off-label. Off-label uses include treating a condition not indicated on the label, or treating the indicated condition but varying the dosing regimen or the patient population. Manufacturer promotion of off-label uses constitutes misbranding. See 21 U.S.C. § 352.

Central to this litigation is that what a manufacturer may

lawfully claim that a drug does under the statutory and regulatory scheme, and what a physician may prescribe a drug for, do not match. Once a drug has been approved by the FDA for marketing for any use, the actual prescription choices regarding those drugs are left to the discretion of the physician. See, e.g., 59 Fed. Reg. 59820, 59821 (1994) (noting that the agency has restated this policy on numerous occasions). A physician may prescribe an approved drug for any medical condition, irrespective of whether FDA has determined that the drug is safe and effective with respect to that illness. That physicians may presently prescribe off-label is not in dispute. See Defendants' Response to Plaintiff's Statement of Material Facts ¶ 9 (noting that off-label prescribing is appropriate in the context of the physician-patient relationship); see also Deposition of William K. Hubbard, Associate Commissioner for Policy Coordination at 59-61 (March 21, 1996) ("Hubbard Deposition"). The FDA contends that it accepts the practice of off-label use by physicians as part of its enforcement discretion, see Defendants' Response to Plaintiff's Statement of Material Facts ¶2; Defendants' Reply to Plaintiff's Memorandum in Opposition at 6 ("Defendants' Reply Memorandum"), though it appears to be an open question as to whether the FDA could currently regulate this aspect of the practice of medicine if it wished to do so.

B. The Pros & Cons of Off-Label Use

Whether characterized as either "the standard of care" or "treacherous," off-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine. See, e.g., Off-Label Drugs, Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies, GAO/PEMD-91-14 at 5 (Sept. 1991) ("GAO Report") (noting that the use of off-label treatments is widespread). The precise extent upon which physicians rely upon off-label uses is disputed by the parties. A study cited by FDA concludes that off-label prescribing for the 64 most frequently prescribed drug products is low -- constituting only 4.7% of all prescriptions for patented drugs, and 2.0% for off-patent drugs. See Off-Label Use Associated With the Prescribing of the Most Frequently Used Drug Products in the United States, 1995 (unpublished draft, May 24, 1996) at 4. However, when one looks to specific areas of medicine, the picture as to off-label use changes dramatically. The General Accounting Office Report looking at anti-cancer drugs found that 25% of anticancer drugs were prescribed off-label and 56% of cancer patients were given at least one drug off-label. See GAO Report at 4. These uses are especially prevalent when the cancer has reached an advanced stage. Off-label prescribing is also common in pediatrics, where drug manufacturers are justifiably reluctant to subject children to experimental clinical trials. See Hubbard Deposition at 77. Even the FDA acknowledges that in some specific and narrow areas of medical practice, practitioners

consider off-label use to constitute the standard of good medical care. See Defendants' Response to Plaintiff's Statement of Material Facts ¶ 4; Deposition of Byron L. Tart, Director, Promotion and Advertising Policy Staff (March 15, 1996) at 153 ("Tart Deposition") (stating that public health may benefit from off-label uses in some circumstances).

As off-label uses are presently an accepted aspect of a physician's prescribing regimen, the open dissemination of scientific and medical information regarding these treatments is of great import. The FDA acknowledges that physicians need reliable and up-to-date information concerning off-label uses. "[M]ore generically, we certainly believe it's very appropriate for physicians to get information about off-label uses from the many sources that they get them. And, of course, they get them from CME; they get them from on-line databases; they get them through textbooks; they get them through discussions with colleagues; they get them through going to a medical center and grand rounds. . . . FDA does not desire or intend to interfere with that process." Hubbard Deposition at 62-63; Defendants' Memorandum of Points and Authorities in Opposition to Plaintiff's Motion for Summary Judgment at 21 ("Defendants' Opposition Memorandum"). The need for reliable information is particularly acute in the off-label treatment area because the primary source of information usually available to physicians -- the FDA approved label -- is absent. See Defendants' Response to

Plaintiff's Statement of Material Facts ¶ 12 (noting that labeling is unavailable for off-label uses); Declaration of Robert Temple, M.D. ¶ 8 ("Temple Declaration") (noting that some information concerning new uses will not be reflected in the approved labeling and that "[p]hysicians are completely free to consider this information and to rely on it in making treatment decisions").

It is not the case however, that off-label prescription practices are wholly unproblematic. Off-label uses have, in some circumstances, proven to be harmful. For example, in the 1980's, physicians began to prescribe, off-label, two anti-arrythmic drugs, encainide and flecainide, to treat minor disturbances in patients who had recently had heart attacks. Patients who took these drugs had a two-and-one-half fold increase in mortality, and estimates of the total number of deaths attributable to this off-label 'treatment' range from 3,000 to 10,000 patients per year. See Temple Declaration at ¶ 21 (also noting the absence of promotion by sponsors). Even in cases in which the off-label use is not "toxic," prescribing a drug that is merely not effective may be no less harmful, because the ineffective prescription regimen will have been substituted for an effective one. See id. ¶ 22 (addressing another example concerning the off-label use of "calcium channel blockers" which subsequently proved to be ineffective, which meant that patients were being deprived of the more effective on-label treatment).

In light of the problems that have arisen out of off-label prescription practices, the FDA, consistent with its mission to protect the public health, claims that it must develop solutions. The agency notes that "the ordinary citizen here has little ability to protect himself or herself from the potential harm associated with unproven uses of drugs and devices. For this reason, FDA has been charged with preventing such harm." Defendants' Opposition Memorandum at 20. (citing United States v. Dotterweich, 320 U.S. 277, 280 (1943)).

C. The Guidance Documents and the Food and Drug Modernization Act

1. Continuing Medical Education (CME) Guidance

In the late 1980's, drug and device companies greatly increased the resources devoted to sponsoring CME seminars. Concerns about the promotional practices of drug manufacturers caught the attention of Congress, which conducted hearings in 1990 to investigate the matter. Among the issues addressed in those hearings was manufacturers' promotion of unapproved claims for approved products. See Advertising, Marketing and Promotional Practices of the Pharmaceutical Industry, 1990: Hearing Before the Senate Committee on Labor and Human Resources, 101st Cong. 2, 5, 8-13 (1990) ("Pharmaceutical Hearings").

In response, FDA developed a Draft Concept Paper that endeavored to identify instances in which the industry could

support scientific and educational programs that addressed off-label uses without violating the Food and Drug Act, which proscribes the misbranding of drugs. However, this concept paper, in defendants' words, "generated even more confusion." Defendants' Opposition Memorandum at 14. After meeting with representatives of the drug and device industry and CME providers, FDA published a Draft Policy Statement on Industry Supported Scientific and Educational Activities, 57 Fed. Reg. 56412 (1992) which again attempted to describe elements that would be significant in determining when a manufacturer-supported program inappropriately promoted off-label uses. The focus of FDA's inquiry was whether the discussion of off-label use was independent of the promotional influence of the sponsoring manufacturer. After receiving and reviewing all comments with regard to the Draft Policy Statement (including a citizen's petition submitted by plaintiff Washington Legal Foundation), the FDA revised its guidance and published the final guidance on December 3, 1997. See 62 Fed. Reg. 64074 (1997).

In the final guidance, the FDA recognized the importance of supporting the full exchange of views in scientific and educational discussions, "including discussions of unapproved uses." Id. at 64095. The guidance was designed to distinguish between those situations in which CME is "independent from the substantive influence of the supporting company," and therefore not subject to regulation, as opposed to when the manufacturer is

in a position to influence the presentation of information, "or otherwise transform an ostensively independent program into a promotional vehicle." Id. The FDA developed twelve factors to consider in evaluating programs and activities to determine "independence" which include: who controls the content and selects presenters and the moderator; whether there is meaningful disclosure as to the company's funding and whether unapproved uses will be discussed; the focus of the program, such as whether the central theme is on one product; the relationship between supporting companies and the CME provider; audience selection; opportunities for meaningful discussion and questioning; dissemination of information; ancillary promotional activities; and any complaints raised by the provider, presenters or attendees regarding attempts by the supporting company to influence content. Id. at 64097-99. Additionally, while not required, a written agreement between the provider and the supporting company "can provide valuable evidence as to whether an activity is independent and non-promotional." Id. at 64099. This written agreement is intended to demonstrate that the sponsoring company has no involvement in the CME seminars such that it might influence the content, and that the provider is solely responsible for designing and conducting the activity.

2. Enduring Materials Guidance Documents

The second set of Guidance Documents concern the

distribution of enduring materials -- textbook excerpts and article reprints from medical and scientific journals. See 61 Fed. Reg. 52800 (1996). These Guidances restrict manufacturer distribution of enduring materials when the publications address off-label uses for the company's previously approved products. Similar to the CME Guidance, the FDA noted the need to "strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses." Id.

As to sponsor/manufacturer distribution of reprints of professional journal articles, the Guidance requires that the principal subject of the article should be the use(s) or indication(s) that has been approved by the FDA, and the article should report the initial study by the FDA on that approved use; that the reprint should be from a bona-fide peer-reviewed journal; that any effectiveness rates, data, analyses, uses, regimens and the like that are different from the approved labeling shall be prominently stated on the face of the reprint; and that the information shall disclose all material facts and shall not be false or misleading. Id. at 52801. It is largely the first requirement with which plaintiff takes issue.

As to reference texts (medical textbooks and compendia), the work may not have been written, edited, excerpted or published specifically at the request of a drug, device or biologic firm,

unless the text was prepared in a manner that results in a balanced presentation; the content may not have been reviewed, edited or significantly influenced by the manufacturer; the text should not be available primarily through the manufacturer -- it should be generally available in other outlets such as bookstores; and, the reference text should not focus on any particular drug and device, "nor should it have a significant focus on unapproved uses of the drug(s), device(s) or biological(s)." Id.

Notably, these restrictions on the dissemination of enduring materials apply only when the drug manufacturer or sponsor seeks to initiate distribution of the materials. Dissemination of article reprints and reference texts that would otherwise violate the Guidances are permissible when that distribution is responsive to a physician's inquiry. See Tart Deposition at 53-54. The court will return to this point in greater detail in evaluating the merits of the case.

3. The Food and Drug Modernization Act of 1997

On November 21, 1997, President Clinton signed into law the Food and Drug Modernization Act of 1997, Pub L. No. 105-115, 111 Stat. 2296 (to be codified at 21 U.S.C. § 551, et seq.). These Amendments differ from the Guidances in that they will permit manufacturer distribution of written information concerning the safety, effectiveness or benefit of an unapproved use of a

previously approved drug under specified conditions. The most notable condition is that the manufacturer must submit an application to have the new use approved by the FDA, or certify that such an application will be submitted within six months after the date of the initial dissemination. See § 551(b). The statute also directly addresses physician-initiated inquiries, as it states, “Nothing in section 551 shall be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner.” See § 557(a). The legislation does not address CME seminars.

The 1997 Modernization Act will become effective no later than one year from the date of enactment, or upon the Secretary’s issuance of final regulations. See id. § 557(d). Consequently, the October 1996 Guidance Documents will be superseded by statute at that time.

## II. ANALYSIS

### A. Summary Judgment

Fed. R. Civ. P. 56(c) provides that, "summary judgment shall be rendered forthwith if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." The rule provides that "the mere existence

of some alleged factual dispute between parties will not defeat an otherwise properly supported motion for summary judgment; the requirement is that there be no genuine issue of material fact." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-248 (1986); Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986).

B. Classification of Manufacturer Sponsorship of CME Seminars and Distribution of Enduring Materials Under Current First Amendment Jurisprudence

The threshold question that this court is called upon to answer is how to classify the “speech” at issue. Plaintiff argues that it is scientific and academic speech, which is entitled to the highest level of First Amendment protection. Defendants challenge this assertion by first making a somewhat difficult to discern argument that the Guidance Documents regulate conduct. A closer examination demonstrates that what the FDA is actually contending is that because the federal government has the broad power to regulate the pharmaceutical industry, the Guidances are incidental encroachments upon speech and entirely compatible with the First Amendment. In the alternative, FDA claims that the Guidance Documents at most regulate commercial speech, which is subject to a more relaxed inquiry than core First Amendment speech.

1. Speech or Conduct?

FDA's first contention -- that the Guidance Documents are a restraint upon conduct and not upon speech -- may be addressed quickly. There is little question that the relevant "conduct" is the off-label prescription of drugs by physicians. The distribution of enduring materials and sponsorship of CME seminars addressing and encouraging that conduct is speech. Mailing enduring materials and/or discussing off-label uses is not inherently "treacherous"; it is only treacherous (if at all) to the extent that physicians choose to pay attention to the message communicated and alter their prescription practices accordingly. As plaintiff's counsel aptly noted at oral argument, the activities at issue in this case are only "conduct" to the extent that moving one's lips is "conduct," or to the extent that affixing a stamp and distributing information through the mails is "conduct."

FDA clearly recognizes the difference between speech and conduct in noting that "[t]hroughout its papers WLF repeatedly mistakes actual off-label use by physicians with the promotion of off-label use by manufacturers . . . FDA's concerns are directed only to the latter." Defendants' Reply Memorandum at 6 (emphasis added). See also id. at 20 ("the Guidance Documents apply only to those situations in which manufacturers 'cross the line' between education and promotion"). This court is hard pressed to believe that the agency is seriously contending that "promotion" of an activity is conduct and not speech, or that "promotion" is

entitled to no First Amendment protection. There may certainly be a "line" between education and promotion as regards a drug manufacturer's marketing activities, but that is the line between pure speech and commercial speech, not between speech and conduct. Clearly, defendants do not truly subscribe to this point of view, as they note that "[i]t is the promotional connection with the company that is key", followed by a cite to Bolger v. Youngs Drug Products Corp., 463 U.S. 60, 67 (1983), which, of course, concluded that the promotional activity at issue was to be analyzed as commercial speech. See Defendants' Opposition Memorandum at 21.

2. Do the Guidance Documents Address Fully Regulable Speech Not Covered by the First Amendment Because the Food and Drug Industry is Extensively Regulated?

The FDA next asserts that the speech regulated by the Guidance Documents falls outside of the ambit of the First Amendment because of the federal government's extensive power to regulate the pharmaceutical industry through the Pure Food and Drug Act, 21 U.S.C. § 331 et seq. See 62 Fed. Reg. at 64077-78; Defendants' Opposition Memorandum at 19-22. The agency claims that "FDA is well within its statutory authority to take such actions as are necessary to ensure that drugs and devices comply with the approval requirements of the [Food and Drug] Act." Defendants' Reply Memorandum at 8. ("Defendants' Reply Memorandum"). In support of this argument, the FDA first looks

to Ohralik v. Ohio State Bar Ass'n, 436 U.S. 447, 456 (1978), which notes that "[n]umerous examples could be cited of communications that are regulated without offending the First Amendment" such as information about securities, corporate proxy statements, the exchange of price and production information among competitors in antitrust regulation, and employer's threats of retaliation for the labor activities of employees. (citations omitted). FDA also notes Ohralik's pronouncement that "the State does not lose its power to regulate commercial activity deemed harmful to the public whenever speech is a component of that activity." Id. See also Dun & Bradstreet, Inc. v. Greenmoss Builders, Inc., 472 U.S. 749, 759 n.5 (1985) (noting that certain types of communications may be regulated without offending the First Amendment). The FDA also directs the court's attention to Securities & Exchange Comm'n v. Wall Street Publ'g Inst., Inc., 851 F.2d 365, 373 (D.C. Cir. 1988), in which this circuit concluded that regulation of the exchange of information in the securities industry was subject only to limited First Amendment scrutiny. In so holding, the Court of Appeals stated that "the government may have the power to regulate Stock Market Magazine, not because the articles are 'commercial speech,' but rather because of the federal government's broad powers to regulate the securities industry." Id. at 372. The Court of Appeals went on to note that "[s]peech relating to the purchase and sales of securities, in our view, forms a distinct category of

communications in which the government's power to regulate is at least as broad as with respect to the general rubric of commercial speech." Id.

The court finds that the cases relied upon by FDA do not support its position here. First, the argument that a certain subset of speech may be considered completely outside of the First Amendment framework because the speech occurs in an area of extensive government regulation is a proposition whose continuing validity is at best questionable in light of the Supreme Court's most recent commercial speech cases. Ohralik, of course, predated the seminal commercial speech case of Central Hudson Gas and Electric Corp. v. Public Service Comm'n of New York, 447 U.S. 557 (1980), by three years. Since the Central Hudson decision, the Supreme Court has consistently applied a speech analysis -- whether under the pure speech or commercial speech framework -- to cases involving statutes and/or regulations in areas subject to extensive state or federal regulation. See, e.g., Rubin v. Coors Brewing Co., 514 U.S. 476 (1995) (alcohol labeling); Turner Broadcasting System, Inc. v. FCC, 512 U.S. 622 (1994) (telecommunications); Pacific Gas and Electric Co. v. Public Utilities Comm'n of California, 475 U.S. 1 (1986) (utilities); Friedman v. Rogers, 440 U.S. 1 (1979) (optometry). Significantly, even in the attorney conduct area -- the area directly at issue in Ohralik -- the court has recently used the commercial speech framework to uphold a restriction on speech.

In Florida Bar v. Went for It, Inc., 515 U.S. 618, 635 (1995), the Court noted, "[p]articularly because the standards and conduct of state-licenced lawyers have traditionally been subject to extensive regulation by the States, it is all the more appropriate that we limit our scrutiny of state regulation to a level commensurate with the 'subordinate position' of commercial speech in the scale of First Amendment values." (citing Board of Trustees of the State University of New York v. Fox, 492 U.S. 469, 477 (1984), quoting Ohralik, 436 U.S. at 456). This statement indicates, if not demands, that areas subject to extensive regulation are to be scrutinized as commercial speech, and not beyond First Amendment scrutiny, as defendants argue.

Any lingering doubt as to whether the government may impose restrictions upon speech without offending the First Amendment merely because it has the authority to regulate the underlying activity was resolved in 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484 (1996). In that case, the Supreme Court expressly rejected the concept embodied in Posadas de Puerto Rico Assoc. v. Tourism Co. of Puerto Rico., 478 U.S. 328 (1986), that because the government had the power to extensively regulate in a certain area (casino gambling) it also had the authority to regulate speech without raising First Amendment concerns. The court held:

> The text of the First Amendment makes clear that the Constitution presumes that attempts to regulate speech are more dangerous than attempts to regulate conduct. That presumption accords with the essential role that the free flow of information plays in a democratic

> society. As a result, the First Amendment directs that the government may not suppress speech as easily as it may suppress conduct.

44 Liquormart, 517 U.S. at 512. In rejecting the "greater includes the lesser" concept of Posadas (or, in reversing the application of the descriptive terms, see id.), the Court expressly stated, "speech restrictions cannot be treated as simply another means that the government may use to achieve its ends." Id. One need only juxtapose this statement with the FDA's claim that merely because it does not regulate off-label use, it need not surrender all enforcement authority to grasp the weakness of the agency's position. FDA's argument that it may freely limit manufacturer dissemination of enduring materials and sponsorship of CME seminars as one among several regulatory options because of the government's broad power to regulate the food and drug industry does not comport with current First Amendment jurisprudence, and therefore must be rejected.

Furthermore, other courts that have assessed the constitutionality of various FDA labeling, advertising and promotion regulations and/or disclosure requirements have proceeded directly to a commercial speech analysis without even considering this "area of extensive regulation" argument advanced by the defendants here. Cases concerning "health claim" labeling restrictions are most instructive, as the agency has advanced a similar "separate area of extensive regulation" rationale in defense of its requirements. See Food Labeling; General

Requirements for Health Claims for Food, 58 Fed. Reg. 2478, 2525 (1993). In Nutritional Health Alliance v. Shalala, 953 F. Supp. 526 (S.D.N.Y. 1997) plaintiffs challenged the constitutionality of a series of regulations dictating that any claim relating a particular nutrient to prevention of a particular disease or health condition had to be supported by "significant scientific agreement" among qualified experts before the manufacturer could label the product with that claim. See 21 C.F.R. § 101.14. The court concluded that this regulation should be analyzed as commercial speech under the Central Hudson test. See id. at 529. Other health claim regulation challenges have been resolved using the commercial speech framework. See Pearson v. Shalala, Civ. A. No. 95-1865 (GK) (D.D.C. Jan. 12, 1998) (using the commercial speech framework to uphold FDA regulations); National Council for Improved Health v. Shalala, 893 F. Supp. 1512, 1516-17 (D. Utah 1995) (noting that a facial challenge to the labeling regulations implicated the First Amendment, and employing the Central Hudson framework to determine if the regulations infringed free speech), vacated on other grounds, 122 F.3d 878 (10th Cir. 1997). Also, in United States v. General Nutrition, Inc., 638 F. Supp. 556, 562 (W.D.N.Y. 1986), the court concluded that labeling is "clearly commercial speech."

In a similar vein, in Federal Trade Comm'n v. Brown & Williamson Tobacco Corp., 778 F.2d 35 (D.C. Cir. 1985) the D.C. Circuit was presented with a First Amendment challenge to the

Federal Trade Commission's requirement that all claims as to milligram tar ratings had to be substantiated through the FTC or an FTC-approved methodology. The validity of the injunction against the tobacco company was analyzed under the Central Hudson test. See id. at 43. Similarly, in Association of Nat'l Advertisers, Inc. v. Lungren, 44 F.3d 726, 728-29 (9th Cir. 1994), a California statute making it unlawful for a manufacturer to claim that products were "ozone friendly," "biodegradable," "photodegradable," "recyclable," or "recycled" unless that product met the statutory definition of those terms was held to implicate commercial speech.

In light of the fact that analytically similar cases challenging regulations on labeling and promotion have not adopted the FDA's stance that the First Amendment is not violated because "the Guidance Documents are merely an outcome of the overall statutory scheme," Defendants' Reply Memorandum at 10, and in light of prevailing First Amendment speech doctrine, in particular 44 Liquormart, this court finds that the Guidance Documents are subject to First Amendment scrutiny.

3. Pure Speech or Commercial Speech?

Having concluded that the Guidance Documents are restrictions upon speech, and that the speech must be analyzed under a First Amendment framework, the next inquiry is as to

whether manufacturer distribution of enduring materials and sponsorship of CME seminars discussing off-label uses are pure speech or commercial speech. As a preliminary matter, the court notes that the aforementioned health claim labeling cases consistently utilized the commercial speech framework.

The resolution of this question is not an easy one, as the communications present one of those "complex mixtures of commercial and non-commercial elements." Bolger, 463 U.S. at 81 (Stevens, J. concurring). Typical "commercial speech" is authored and/or uttered directly by the commercial entity that wishes to financially benefit from the message. A purveyor of goods or services makes claim about his products to order to induce a purchase. In this instance, by contrast, the speech that the manufacturers wish to "communicate" is the speech of others -- the work product of scientists, physicians and other academics.

It is beyond dispute that when considered outside of the context of manufacturer promotion of their drug products, CME seminars, peer-reviewed medical journal articles and commercially-available medical textbooks merit the highest degree of constitutional protection. Scientific and academic speech reside at the core of the First Amendment. See, e.g., Keyishian v. Board of Regents, 385 U.S. 589, 603 (1967); Board of Trustees of Leland Stanford Junior University v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991) ("It is equally settled, however, though

less commonly the subject of litigation, that the First Amendment protects scientific expression and debate just as it protects political and artistic expression."). Plaintiff claims that because this speech merits full protection when uttered by a scientist or academic, the level of constitutional scrutiny should not change merely because a corporation wishes to enhance the distribution of that message. Cf. First National Bank of Boston v. Bellotti, 435 U.S. 765, 784 (1978) (holding that the expression of views on matters of public importance does not lose First Amendment protection merely because a corporation seeks to utter the speech); New York Times v. Sullivan, 376 U.S. 254, 266 (1964) (noting that statements do not lose constitutional protection because they are presented in the form of a paid advertisement). Furthermore, plaintiff notes that even though a manufacturer may "have an economic motivation" for dissemination of the speech, that is insufficient, without more, to transform the enduring materials and CME seminars into commercial speech. Bolger, 463 U.S. at 67. Finally, because the manufacturer is disseminating information that will be of professional use to a physician whether or not the physician ultimately prescribes (and the patient thereby purchases) the drug at issue, the speech arguably does much "more than just propose a commercial transaction." Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, 425 U.S. 748, 762 (1976); see also id. at 759 (concluding that commercial speech was squarely before the

court because the pharmacist did not wish to report a newsworthy fact).

Plaintiff argues that "there is no evidence that the speech at issue proposes a commercial transaction." Plaintiff's Opposition Memorandum at 13. The court must disagree with this statement. The mechanism by which a commercial transaction may be "proposed" can vary widely. In the consumer goods area, of course, the proposal usually involves a manufacturer making a claim about its product that encourages the purchase of the product. However, there are certainly instances in which a manufacturer promotes and induces the purchase of its product by directing attention to favorable information generated by wholly independent organizations. For example, auto manufacturers often encourage purchase of vehicles by noting that a certain model has been rated #1 in a customer satisfaction survey, or that a trade magazine has pronounced the vehicle "Car of the Year." No one would seriously dispute that an auto dealer was proposing a commercial transaction if he mailed reprints of the customer satisfaction surveys or the magazine articles to past customers who were likely to be looking for a new car in the near future. Similarly, restaurants frequently encourage patronage through promoting favorable magazine reviews -- and even go so far as to prepare reprints of these reviews to display in the windows of the establishment. These reprints would likely not merit the same degree of First Amendment protection as a political campaign

poster hanging in the same window.

The peculiarities of the prescription drug industry make dissemination of scientific research results an especially important and prevalent marketing tool. Though patients are the end-point purchasers of prescription drugs, their choices are constrained by physicians because a patient can only obtain the manufacturer's products with a physician's authorization -- a prescription. To the extent that physicians are the gatekeepers to sales, the marketing efforts must be directed at them. That fact, combined with the reality that a typical patient is unlikely to strongly challenge a physician's recommendation concerning a prescription, or have the education and background to make informed choices among equally effective treatments, means that the treating physician is going to be target of much of the pharmaceutical industry's attention.

And, despite the FDA's occasional statements in its briefs to the contrary, physicians are a highly educated, professionally-trained and sophisticated audience. In making prescribing decisions, doctors want (and need) to know first and foremost if the drug is the most safe and effective means to treat the conditions suffered by the patients. One critical source of that information is the research product of other physicians, scientists and academics. Manufacturers, keenly aware of this, want to get scientific information demonstrating the efficacy of their products in the hands of physicians. See,

e.g., Pharmaceutical Hearings at 9 (documenting that the money spent on physician symposia increased from $2.72 million in 1974 to $85.92 million in 1988). Defendants have provided this court with substantial evidence that making physicians aware of research concerning their drugs has a positive effect on the number of prescriptions written, which is equal to a positive effect on sales. See Jerry Avorn et al., "Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians," 73 Am. J. Med. 4-8 (1982) (study concluding that a drug company sponsorship of CME events was found to lead to an increase in the purchase of the funding company's products); Marjorie A. Bowman and David L. Pearle, "Changes in Drug Prescribing Patterns Related to Commercial Company Funding of Continuing Medical Education," 4 Journal of Continuing Education in the Health Professions 13, 13-20 (1988). Consequently, there can be little question that the reason that drug manufacturers wish to disseminate enduring materials and sponsor CME seminars is because they believe that such activity will increase the sales volume of their drugs.

So, a compelling question is raised: does speech that would be fully protected as scientific and/or educational speech become transformed into commercial speech, with its reduced level of protection, by the mere fact that a commercial entity seeks to distribute it in order to increase its sales of the product addressed in the speech?

Whether or not a given communication constitutes commercial speech is predicated upon “the 'commonsense' distinction between speech proposing a commercial transaction . . . and other varieties of speech." Bolger, 463 U.S. at 64 (quoting Ohralik, 436 U.S. at 455-56); see also City of Cincinnati v. Discovery Network, Inc., 507 U.S. 410, 423 (1993); Board of Trustees of the State University of New York v. Fox, 492 U.S. 469, 473-74 (1989). Bolger directs a reviewing court to look to three factors in determining whether a form of communication merits full or reduced First Amendment protection. These factors are: (1) whether the speech is concededly an advertisement; (2) whether the speech refers to a specific product; and (3) whether the speaker has an economic motivation for disseminating the speech. Bolger, 463 U.S. at 66. If all three factors are present, the speech “may properly be characterized as commercial speech.” Wall Street Publishing, 851 F.2d at 372 (citing Bolger, 463 U.S. at 66-67). See also Association of National Advertisers, 44 F.3d at 728; U.S. Healthcare v. Blue Cross of Greater Philadelphia, 898 F.2d 914 (3d Cir. 1990).

The application of these factors directs the conclusion that manufacturer sponsorship of CME seminars at which the sponsor’s products are discussed and the distribution of enduring materials focusing on the manufacturer’s product are properly classified as commercial speech. Despite plaintiff’s protestations to the contrary, the activities at issue do “propose a commercial

transaction" as they suggest that a physician should prescribe -- and a consumer therefore will purchase -- the subject drug. Virginia State Board of Pharmacy, 425 U.S. at 762.

As to the first prong of Bolger, the court finds that these activities are advertisements as that term is commonly understood. An advertisement "call[s] public attention to, especially by emphasizing desirable qualities so as to arouse a desire to buy or patronize." Webster's Ninth New Collegiate Dictionary (1990). Through distributing enduring materials and sponsoring CME seminars, drug manufacturers call a physician's attention to the subject drug product, show that the drug effectively treats a certain condition (emphasize a desirable quality) in the hopes that the physician will prescribe (buy or patronize) the drug. The fact that an effective means for accomplishing that goal is through providing the academic research results generated by others does not mean that the activity is not an "advertisement." As to the second prong, the textbook excerpts, article reprints, and symposia presumptively refer to a specific product -- the drug that is the subject of the off-label use. Were pharmaceutical manufacturers attempting to provide free yearly subscriptions to the Journal of American Medicine, or seeking to support CME regardless of whether their products would ultimately be addressed, a different conclusion might be compelled, as the speech would be closer to a public service. But, as long as the manufacturer seeks to disseminate

information centered upon its product, this prong of the test is satisfied. Finally, the pharmaceutical companies clearly have an economic motivation for providing the information; as explained in some detail previously, the promotional efforts at issue have a positive effect on a physician's prescription practices and therefore on sales. See Avorn at 4-8; Bowman & Pearle at 13-20.

The facts from Bolger provide considerable support for the conclusion that manufacturer dissemination of enduring materials and sponsorship of CME seminars is properly classified as commercial speech. Among the informational pamphlets that Young's Drug Products wished to mail included one entitled "Plain Talk About Venereal Disease," which discussed condom use without any specific reference to the varieties manufactured by the company. Bolger, 463 U.S. at 67 n. 13. The court still concluded that the pamphlet constituted commercial speech. In the instant case, one could similarly argue that the reprints and seminars are merely informational, and the fact that more prescriptions are written as a result of the manufacturer's efforts is no different than if more prescriptions were written as a result one physician referring a peer to an article. However, because this information is in fact supplied by the manufacturer, and because the primary purpose for supplying the information is to encourage the purchase of the featured product, the court must conclude that the speech is "entitled to the

qualified but nonetheless substantial protection accorded to commercial speech." Id. at 68.

Furthermore, this conclusion makes sense when one considers the rationale underlying the Supreme Court's determination that less exacting review is to be afforded commercial speech. The general purpose of the commercial speech doctrine is to "protect consumers from misleading, deceptive or aggressive sales practices." 44 Liquormart, 517 U.S. at 501; Discovery Network, 507 U.S. at 426 (noting that it is the state's interest in preventing commercial harms that allows the government to subject commercial speech to greater restrictions). At first glace, it is hard to fathom how dissemination of enduring materials or sponsorship of CME seminars could constitute a deceptive or aggressive sales practice. After all, the physician may obtain the same information from sources other than the manufacturer, and the information is clearly not subject to reduced First Amendment scrutiny in their hands. However, to understand the potential for harm one must look both at the promotional activity in the aggregate and to the substantial resources available to manufacturers. For any given off-label prescription drug treatment, there may be a wide variety of scientific research data available, some of which concludes that the off-label treatment is effective, some of which concludes that the treatment is not. On the other hand, manufacturers will likely only seek to disseminate information that presents their product

in a favorable light.[2] That fact, combined with the considerable financial resources available to pharmaceutical companies, means that findings concluding that a drug effectively treats a condition is more likely to reach a physician than studies reaching the opposite conclusion. Therefore, physicians could be led to believe that a certain drug is safe and effective because a manufacturer has found, and aggressively promoted, "the one" article that supports use of their drug, even if there exists considerable evidence to the contrary. The potential to mislead, and the harm that could result, convinces this court that it is permissible to "depart from the rigorous review that the First Amendment generally demands." 44 Liquormart, 517 U.S. at 501.

For the aforementioned reasons, this court finds that the speech addressed by the Guidance Documents is properly classified as commercial speech.

C. The Commercial Speech Test Applied

Having concluded that manufacturer distribution of enduring materials and suggesting content or speakers for CME seminars in which the focus is on the sponsor's product is properly classified as commercial speech, this court will now analyze the

[2]If an article or textbook excerpt concluded that a certain off-label treatment regimen was either ineffective or dangerous, and a competing drug manufacturer sent reprints of that article to physicians on an "informational" basis, the court wonders whether the manufacturer would vigorously defend his competitor's act as "meriting the highest form of First Amendment protection."

constitutionality of the Guidance Documents under Central Hudson's four-prong test.

1. The Speech Is Neither Unlawful Nor Inherently Misleading

"[T]he First Amendment does not protect commercial speech about unlawful activities." 44 Liquormart, 517 U.S. at 497 n.7 (citing Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376 (1973)). "False, deceptive, or misleading advertising remains subject to restraint." In re R.M.J., 455 U.S. 191, 200 (1982); see also Virginia State Board of Pharmacy, 425 U.S. at 771-72 ("[u]ntruthful speech, commercial or otherwise, has never been protected for its own sake.") (citations omitted).

The speech here addresses using FDA-approved drugs to treat conditions and in treatment regimens other than those set forth in the label approved by the FDA. As explained above, FDA does not purport to regulate the practice of medicine, and the agency has long recognized that, in general, physicians may use an approved drug or device for an unapproved use. See 59 Fed. Reg. 59280, 59281 (1994) ("once a [drug] product has been approved for marketing, a physician may prescribe it for uses in treatment regimens or patient populations that are not included in the approved labeling"); see also Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26720, 26733 (1983). It is obvious that the off-label prescription of

previously approved drugs by physicians is presently lawful activity.

In claiming that the speech at issue involves "illegal activities," the FDA does not seriously press any argument that off-label prescriptions are illegal. Rather, the agency directs attention to the statutory basis for the Guidance Documents and asserts that the speech cannot survive the first prong of the Central Hudson test because a drug or device is considered to be misbranded as a matter of law if it is promoted by the manufacturer for an off-label use. See 21 U.S.C. § 352. Therefore, when a manufacturer disseminates information about a drug product that diverges from the treatments included on the label, that manufacturer may be engaged in misbranding, which is illegal. See, e.g., 62 Fed. Reg. at 64079. However, the tautological nature of this argument exposes its shortcomings. The proper inquiry is not whether the speech violates a law or a regulation, but rather whether the conduct that the speech promotes violates the law. The Supreme Court formulates the restriction this way: "[T]he First Amendment does not protect commercial speech about unlawful activities." 44 Liquormart, 517 U.S. 497 n.7 (emphasis added). Were the FDA's characterization of what constitutes "lawful activity" accurate, First Amendment protections for commercial speech could be all but eviscerated by the government: First Amendment challenges to speech restrictions would be defeated by noting that Congress had made

the speech illegal, and therefore unlawful activity is at issue. The flaw in the FDA's reasoning is perhaps best demonstrated by example. In Rubin v. Coors Brewing Co., 514 U.S. 476 (1995) the challenged statute prohibited the display of alcohol content on beer labels. Under the FDA's definition of "illegal activity," the statute would have been a satisfactory restriction on commercial speech because printing alcohol content on beer labels would render the product "misbranded."

It is clear that when the Supreme Court declares that the First Amendment does not protect illegal activity, it is referring to the conduct that the speech is promoting (e.g., prostitution, counterfeiting, narcotic use, and the like), and not the speech subject to the restriction. Therefore, only at such time as off-label prescriptions are proscribed by law could the FDA legitimately claim that speech at issue addresses "illegal activities."

Whether the speech subject to the restrictions in the Guidance Documents is truthful and non-misleading presents a somewhat closer question. Notably, speech that is merely "potentially misleading" does not render it able to be proscribed under the commercial speech test without further analysis. "If the 'protections afforded commercial speech are to retain their force, we cannot allow rote invocation of the words 'potentially misleading' to supplant [the government's burden].'" Ibanez v.

Florida Department of Business and Professional Regulation, 512 U.S. 136, 146 (1994) (internal citation omitted). In order to end the Central Hudson analysis on the first prong, the speech must be "inherently misleading," which is defined in Central Hudson as "more likely to deceive the public than to inform it." Central Hudson, 447 U.S. at 563 (citations omitted); see also In re R.M.J., 455 U.S. at 202. Whether speech is "inherently misleading" depends upon, inter alia, the "possibilities for deception," see Friedman, 440 U.S. at 13; whether "experience has proved that in fact that such advertising is subject to abuse," In re R.M.J., 455 U.S. at 203; and, "the ability of the intended audience to evaluate the claims made." Id. (quoted in Association of National Advertisers, 44 F.3d at 731.)

In its Summary of Comments proceeding the Final Guidance on CME activities, the FDA affirmatively declared that the scientific and educational activities at issue in this case were not inherently misleading. See 62 Fed. Reg. at 64079 (instead remarking that they were "clearly potentially misleading"). However, in its memorandum in support of its motion for summary judgment, the agency takes a markedly different stance, claiming that the speech is "inherently misleading," and that "the Act prescribes a specific system for determining the 'truth' of claims about drugs and devices." Defendants' Memorandum of Points and Authorities at 32. The FDA was correct the first

time.

In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe. It is certainly the case that by statute, no drug may be introduced or delivered into interstate commerce without FDA approval, and that the claims that a manufacturer may make about a drug through labeling, advertising and other forms of promotion are subject to FDA regulatory authority. However, the conclusions reached by a laboratory scientist or university academic and presented in a peer-reviewed journal or textbook, or the findings presented by a physician at a CME seminar are not "untruthful" or "inherently misleading" merely because the FDA has not yet had the opportunity to evaluate the claim. As two commentators astutely stated, "the FDA is not a peer review mechanism for the scientific community." See Lars Noah & Barbara A. Noah, Liberating Commercial Speech: Product Labeling Controls and the First Amendment, 47 Fla L. Rev. 63, 96 (1995). The agency puts it another way: "[t]he fact that [a use] is not an approved indication should not be viewed [by HCFA] as some sort of determination by FDA that the use is inappropriate or -- is ineffective." See Hubbard Deposition at 141. And, at least one

other court concurs. "Although the Government argues that health claims that have not been FDA approved are inherently misleading, not all potential health claims are misleading; at least some can be presented in a non-misleading fashion." Nutritional Health Alliance, 953 F. Supp. at 529.

Interestingly, and quite significantly, the FDA has a categorically different view on whether article reprints or CME seminars addressing off-label treatments are "inherently misleading" when anyone other than the drug manufacturer is responsible for their dissemination. See Hubbard Deposition at 46 ("only when a drug company gets involved [and the use is promotional]. . . do we have a concern"); Tart Deposition at 155 ("the doctor should have as much information as he feels necessary to use that drug or device on his patient, and that physician is obligated to get that information"). For example, in the Reprint Guidance, it cannot go unnoted that the FDA has no objection to manufacturer distribution pursuant to a request by a physician, or distribution from any source other than the drug manufacturer. "Defendants' witnesses have made clear that physicians are free to receive information about off label-uses from numerous other sources . . . . " Defendants' Reply Memorandum at 20; see also Defendants' Response to Plaintiff's Statement of Material Facts ¶ 19. Obviously, the exact same journal article or textbook reprint cannot be inherently conducive to deception and coercion when it is sent unsolicited,

yet of significant clinical value when mailed pursuant to a request. Additionally, the FDA makes no effort to regulate discussion of off-label uses at a CME seminar when there is no pharmaceutical company involvement, but a seminar in which a company does not suggest the content or the speakers could be just as convincing as to the possible benefits of an off-label use, if not more so, because an attendee is less likely to view such a presentation with a jaded eye. Whether or not the manufacturer plays a role in the dissemination, scientific and academic speech concerning off-label use is either "treacherous anecdotal evidence," or it is not. It is clear that it is not. Were the materials at issue here either actually or inherently misleading, one would have to conclude that the FDA would be derelict to not proscribe dissemination under all circumstances.

FDA notes that another court in this district has apparently considered whether all claims subject to an FDA regulatory scheme are, by definition, "inherently misleading" by virtue of the fact that the FDA has not evaluated those claims. In Pearson v. Shalala, Civ. A. No. 95-1865 (GK) (D.D.C. Jan 12, 1998), the court addressed a constitutional challenge to FDA regulations requiring agency authorization before a manufacturer could label dietary supplements with health claims. In upholding the regulations, the court concluded that "[f]or a health claim label not to be inherently misleading the FDA must find it to be

supported by significant scientific agreement." Id. at *17. However, that statement must be considered in the context in which it was made. The health claims that the manufacturer wanted to include on the label had already been proven by the FDA to be untruthful. See id. at *18-20. The court carefully reviewed each of the four claims, why they were in fact false, and then noted that "[g]iven that each of these claims failed to meet the 'significant scientific agreement' standard, the FDA found each to be inherently misleading." Id. at 20. This court agrees that a regulatory agency clearly may proscribe speech that the agency has proven to be actually misleading and untruthful under the Central Hudson framework. Nothing in this opinion limits the FDA's ability to strictly enforce any rule, regulation or guidance that sanctions the dissemination of information that is actually false or misleads. Second, and more significantly, the Pearson court went on to note that, "in the unlikely event that Plaintiffs were able to propose health claims that were not misleading, even though they could not meet the 'significant scientific agreement' standard [Central Hudson would still not be satisfied]." Id. at *20. This statement indicates a recognition that a claim may not have obtained FDA approval and nonetheless be non-misleading. Also, it should be noted that the health claims in Pearson were directed towards consumers, id. at 18, whereas here the claims are directed to a professional audience -

- physicians. However, to whatever extent Pearson stands for the proposition that all claims made by scientists and academics are, by definition, "inherently misleading" simply because the findings have not been evaluated by FDA, this court must respectfully disagree.

To categorize the speech at issue here as "inherently misleading" is particularly unsupportable when one considers all the controls available to FDA to ensure that the information manufacturers wish to distribute is scientifically reliable, and therefore less likely to even be "potentially misleading." Pursuant to the order issued this day, the FDA may:

> 1. require conspicuous notifications that the uses under discussion have not been approved by the FDA;
>
> 2. require that for article reprints, that the reprint comes from a bona fide peer-review journal, with the term "bona fide peer-review" meaning "a journal that uses experts to objectively review and select, reject, or provide comments about proposed articles. Such experts should have demonstrated expertise in the subject of the articles under review, and be independent from the journal";
>
> 3. require that for textbook reprints, that the textbook is published by a "bona fide independent publisher," with the term "bona fide independent publisher" meaning "a publisher that has no common ownership or corporate affiliation with a pharmaceutical or medical device manufacturer and whose principal business is the publication and distribution of books through normal distribution channels";
>
> 4. require that for CME seminars and symposia, the sponsor must be an "independent program provider," with that term defined as "an entity that has no common ownership or other corporate affiliation with a pharmaceutical or medical device manufacturer, that engages in the business of creating and producing continuing medical educational seminars, programs or other symposia and that is accredited

> by a national accrediting organization pertinent to the topic of such seminars, programs or symposia";
>
> 5. require pharmaceutical and device manufacturers that sponsor or provide financial support for the dissemination or redistribution of articles or reference textbooks or for seminars and symposia that include references to uses of drugs or medical devices other than those approved by the FDA to disclose (i) its interest in such drugs or devices, and (ii) the fact that the use discussed has not been approved by the FDA;
>
> 6. enforce any rules, regulations, guidances, statutes or other provisions of law that sanction the dissemination or redistribution of material that is false or misleading.

Compare Peel v. Attorney Registration and Disciplinary Comm'n of Illinois, 496 U.S. 91, 111 (1990) (Marshall, J., concurring) (noting that the government may not "ban potentially misleading speech if narrower limitations could be crafted to ensure that information is presented in a nonmisleading manner") (emphasis in original). These controls would greatly circumscribe the possibility that untruthful or misleading information would be disseminated by manufacturers.

This court finds that the Guidance Documents address speech that is directed toward lawful activity and that is not misleading. Therefore, the first prong of the Central Hudson test is satisfied.

2. The Government's Interest is Substantial

Under Central Hudson, the second inquiry is whether the interest asserted by the government is substantial. The Supreme Court has consistently held that the government has a substantial

interest in protecting the health and safety of its citizens. See, e.g., Posadas, 478 U.S. at 341. There are few, if any, more important functions performed by any regulatory agency than the function this case concerns -- ensuring that when a citizen takes a prescription drug, that individual has absolute assurance that the product is safe and effective for the condition for which his physician has prescribed it. Any claim that the government's general interest is insufficient under Central Hudson is frivolous.

Within the general category of promoting health and safety, the government describes two more specific interests: 1) ensuring that physicians receive accurate and unbiased information so that they may make informed prescription choices, and, 2) providing manufacturers with ample incentive to get previously unapproved uses on label. As one of these interests is legitimate and the other is not, they will be considered separately.

a. The Government Cannot Justify the Guidances Out of the Fear that Information Will be Misused by Physicians

FDA claims that "the Guidance Documents identify reasonable means to ensure that physicians are not misled . . ." Defendants' Opposition Memorandum at 37, 38. The agency claims that "most physicians, well-educated and experienced though they may be, do not have the resources, experience, or education to

critically evaluate evidence concerning off-label uses. While physicians may believe that they are in a better position than FDA to evaluate off-label claims, both the evidence and the law say otherwise." Defendants' Reply Memorandum at 17. To the extent that the FDA is endeavoring to keep information from physicians out of concern that they will misuse that information, the regulation is wholly and completely unsupportable.

If there is one fixed principle in the commercial speech arena, it is that "a State's paternalistic assumption that the public will use truthful, nonmisleading commercial information unwisely cannot justify a decision to suppress it." 44 Liquormart, 517 U.S. at 497; see also id. at 503 ("The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good"); Virginia State Board of Pharmacy, 425 U.S. at 772 (holding that a state may not completely suppress the dissemination of truthful information about entirely lawful activity because of concern over the effect that the speech will have upon its disseminators and its recipients). To endeavor to support a restriction upon speech by alleging that the recipient needs to be shielded from that speech for his or her own protection, which is the gravamen of FDA's claim here, is practically an engraved invitation to have the restriction struck.

In this instance, the government's notion that the

scientific research product which the manufacturers seek to distribute needs to be withheld for the "good of the recipient" is even more unsupportable than usual. First, it must be noted that the manufacturers are not seeking to distribute this information to the general consumer public, who likely lack the knowledge or sophistication necessary to make informed choices on the efficacy of prescription drugs. Compare Edenfield v. Fane, 507 U.S. 761, 775 (1993) (distinguishing Ohralik because the persons receiving the information from the accountants were sophisticated and experienced executives who understood the CPAs' business services); In re R.M.J., 455 U.S. at 200. Rather, they seek to disseminate this information exclusively to physicians. A physician's livelihood depends upon the ability to make accurate, life-and-death decisions based upon the scientific evidence before them. They are certainly capable of critically evaluating journal articles or textbook reprints that are mailed to them, or the findings presented at CME seminars.[3] Furthermore, the FDA does not question a physician's evaluative skills when an article about an off-label use appears among a group of articles in the New England Journal of Medicine, or when one physician refers a peer physician to a published article he recently perused, or even when a physician requests a reprint from a

[3]This evaluative ability questioned by defendants certainly would be enhanced by the less burdensome alternative discussed in Part II.C.4 -- disclosure that the use under discussion had not been approved by the FDA.

manufacturer. Why the ability of a doctor to critically evaluate scientific findings depends upon how the article got into the physician's hands, or whether a manufacturer suggests speakers or content for a CME seminar, is unclear to this court.

In light of the fact that the Supreme Court has repeatedly rejected governmental attempts to equate less information with better decision-making, and in light of the fact that the FDA does not question a physician's evaluative skills when the information comes from a source other than a drug manufacturer, concerns about a physician's ability to critically evaluate materials presented to him is not a "substantial interest."

b. The Government Does Have a Substantial Interest in Compelling Manufacturers to Get Off-Label Treatments On-Label.

The other substantial interest that the regulations purportedly advance is that they provide an incentive for manufacturers to go through the strict FDA preclinical and clinical trial process to get off-label uses on-label. As explained previously, defendants have proved to this court's satisfaction that dissemination of scientific information on off-label uses is an effective means of influencing physicians to prescribe a drug for a given condition. See Avorn, at 4-8; Bowman & Pearle, at 13-20. Consequently, the dissemination of information demonstrating that a drug is effective has a positive effect upon sales of the drug. But, if the manufacturer's

ability to disseminate any information on a new use for a previously approved drug is made wholly contingent upon FDA approval of that use, the manufacturer will be encouraged, if not compelled, to obtain FDA approval.

Plaintiff appears to take issue with the idea that the government has a substantial interest in requiring manufacturers to get new uses for previously approved drugs on-label. They assert that off-label uses are on whole beneficial to the public health, contending that "the ability to prescribe off-label is essential to saving patients' lives." Plaintiffs' Opposition Memorandum at 22. They cite the large number of off-label prescriptions written by physicians every year, and again state that, even by FDA's own admissions, off-label treatments may constitute the standard of care for some conditions. In sum, plaintiff argues that "the fact that a use is off-label rather than on-label has no necessary correlation to the benefits of that use." Plaintiff's Memorandum in Support of Summary Judgment at 7. WLF then goes on to state:

> Even assuming that this is an arguably legitimate interest [getting new uses on-label], it is hardly compelling and cannot justify the broad restrictions at issue here . . . . FDA admits that many new factors militate against adding new uses to approved labeling, including, inter alia, the unavoidable time lapse between scientific discoveries and the submission of an application, the sometimes unjustifiable expense of conducting clinical trials, the substantial delays attendant to agency review of supplemental use applications, and the limited market potential for some

beneficial uses.[4]

Id. at 32. The court reads this statement, and much of plaintiff's briefing about off-label use, as a veiled argument that requiring manufacturers to get new uses on-label does not, on balance, promote public health.

However, whether compelling manufacturers to get new uses on-label is wise government policy when considered against the backdrop of present day medical realities, financial constraints and procedural burdens is a policy question that must be addressed to Congress, not to this court. Congress has concluded that it benefits the public health to require manufacturers to get all uses approved by the FDA. The Supreme Court has held

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[4]At one point in its opposition brief, plaintiff attempts to argue that FDA approval of subsequent uses is discretionary rather than mandatory. WLF states, "[a]s discussed in WLF's initial memorandum, such applications are not required, and there are numerous reasons why they may not be filed in particular circumstances. See WLF Mem. at 5-8 (citing evidence)". See Plaintiff's Opposition at 25. Notably, plaintiff's "evidence" on pages 5-8 of its memorandum of points and authorities consists of its discussion of the prevalence and importance of off-label uses by physicians, but no support for the proposition that a manufacturer may market an off-label use without FDA approval. Fundamental to this entire litigation is the fact that the rules that physicians must follow in prescribing, and those that drug manufacturers must follow in labeling, marketing, and promoting are different. The fact that physicians may prescribe and do prescribe off-label, and that those prescriptions may often be the standard of care, does not mean that manufacturers are not required by statute to get all new drugs evaluated for safety and efficacy for use under the conditions prescribed, recommended or suggested in the labeling. There is no support for the contention that this approval process is discretionary to the extent that manufacturers may elect not to submit the new use for FDA approval and still label the drug for that use.

that the approval requirement is not subject to exceptions based upon the difficulty of obtaining approval, the cost, or even the conceded benefits of the unapproved use. See United States v. Rutherford, 442 U.S. 544, 557-58 (1979) (rejecting arguments that FDA approval requirements for new uses could be overcome, even when terminally ill patients were to receive the treatments). In light of the fact that Congress has declared that all uses for a drug must be proven safe and effective by the FDA, and has recently reaffirmed that position through the 1997 Food and Drug Amendments, this court finds that this interest -- that off-label uses of previously approved drugs are subjected to the FDA's evaluation process -- is of sufficient importance so as to constitute a "substantial government interest" as contemplated by Central Hudson.

3. The Guidance Documents Directly Advance the Substantial Government Interest in Requiring Manufacturers to Submit Supplemental Applications to Obtain Approval for New Uses

Under the Central Hudson test, commercial speech restrictions must advance the government's interest in "a direct and material way." In Edenfield v. Fane, 507 U.S. 761 (1993), the Court held that, "[t]his burden is not satisfied by mere speculation or conjecture; rather, a governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree." Id. at 770-71.

(citations omitted). What the court must determine is whether the Guidance Documents directly advance the "subsequent approval" interest: do they encourage and/or compel a drug manufacturer to submit previously approved drugs to the FDA for approval of the off-label treatments? While defendants have not presented what this court considers to be substantial evidence on this point, the court still answers this question in the affirmative, in large part based upon the arguments of plaintiff.

That drug manufacturers often would like to avoid having to submit previously approved drugs to the FDA for subsequent approvals is clear. Plaintiff admits that among the reasons drug manufacturers wish to engage in the distribution of enduring materials and sponsorship of CME seminars concerning off-label uses is because of the slow pace of the FDA approval process. See Plaintiff's Memorandum of Points and Authorities at 8. Furthermore, plaintiff notes that "economic considerations also may play a role in determining whether beneficial uses of drugs are submitted for approval." Id. They explain (albeit consistently couched in the terms "FDA recognizes that") that manufacturers may be unwilling to pursue expensive and well-controlled clinical trials if subsequent sales of the drugs are insufficient to cover the costs. And, if a product is no longer protected by patent, a manufacturer will have little incentive to get the new use on-label because generic manufacturers could become instantaneous free-riders on the approval. Id. Finally,

even the pace of FDA approval has economic repercussions because during the time that it takes to get approval, a manufacturer is unable to market the product for the new use, and, given the correlation between marketing efforts and sales, that delay affects the manufacturer's bottom line.

It is clear that manufacturers have incentives to circumvent subsequent approval requirements, but one wonders what incentives they have to obtain them? For a brand-new drug, the incentive is simple: the pharmaceutical company cannot manufacture or introduce the drug into interstate commerce without FDA approval. See 21 U.S.C. § 355(a). However, the drugs subject to off-label prescriptions are already in interstate commerce, so the obvious restriction on conduct is unavailable. Therefore, one of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising and marketing. If a manufacturer is proscribed from distributing enduring materials and/or sponsoring CME seminars that address that manufacturer's product absent FDA approval of that use, that proscription provides a strong incentive to get the use on-label, in light of the connection between marketing and sales.

Because the restrictions on the distribution of enduring materials and involvement with CME do provide an incentive for manufacturers to have previously approved drugs evaluated by the FDA for safety and effectiveness for an off-label use, this court

finds that the restrictions in the Guidance Documents directly advance a substantial interest. See Central Hudson, 447 U.S. at 569.

4. The Guidance Docmuents Are Unconstitutional Because They Are More Extensive than Necessary.

While commercial speech jurisprudence does not require the government to employ the least restrictive means of advancing an interest, the regulating body must make an effort to reasonably fit its means to its end sought. Fox, 492 U.S. at 478 (the means need not be the "single best disposition, but one whose scope is 'in proportion to the interest served.'") (quoting In re R.M.J., 455 U.S. at 203). A commercial speech restriction will fail if it burdens "substantially more speech than necessary." United States v. Edge Broadcasting Co., 509 U.S. 418, 430 (1993) (citing Ward v. Rock Against Racism, 491 U.S. 781, 799 (1989). The court finds that the restrictions in the Guidance Docmuents are considerably more extensive than necessary to further the substantial government interest in encouraging manufacturers to get new uses on-label.

This determination is based in large part upon the fact that there exist less-burdensome alternatives to this restriction on commercial speech. See, e.g., Coors Brewing, 514 U.S. at 490-91. The most obvious alternative is full, complete, and unambiguous disclosure by the manufacturer. See Note, Edmund Polubinski III,

Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of Off-Label Use, 83 Va. L. Rev. 991, 1031 (1997). Full disclosure not only addresses all of the concerns advanced by the FDA, but addresses them more effectively. It is less restrictive on speech, while at the same time deals more precisely with the concerns of the FDA and Congress. See Shapero v. Kentucky Bar Ass'n, 486 U.S. 466, 476 (1988).

First, it assuages concerns that the message communicated is inherently or potentially misleading, or that a physician would be deceived or misled by the speech. That the use discussed therein had not been approved by the FDA would be readily apparent. A physician would be immediately alerted to the fact that the "substantial evidence standard" had not been satisfied, and would evaluate the communicated message accordingly. And, the failure to provide such disclosure would render the communication subject to the full battery of FDA enforcement options, because not including such disclosure when required would clearly render the materials "inherently misleading."

Second, permitting this limited form of manufacturer communication still leaves more than adequate incentives compelling drug manufacturers to get new uses approved by the FDA. As plaintiffs noted at oral argument, it is a very narrow form of manufacturer communication upon which this court is ruling in enjoining enforcement of the Guidance Documents. There

still are enormous differences between the permitted marketing of on-label as opposed to off-label uses. Manufacturers still are proscribed from producing and distributing any internally-produced marketing materials to physicians concerning off-label uses, or from involvement with seminars not conducted by an "independent program provider." Nor may the drug companies initiate person-to-person contact with a physician about an off-label use. Nor may they advertise off-label uses for previously approved drugs directly to the consumer. If a manufacturer wishes to engage in any of these or other marketing techniques, it cannot do so without first obtaining FDA approval of the off-label use. The fact that these adequate incentives still exist to get off-label treatments on-label is central to this court's finding that the First Amendment is violated by the Guidance Documents. Were manufacturers permitted to engage in all forms of marketing of off-label treatments, a different result might be compelled.

Third, to the extent that physicians look to FDA approval as an important (or the exclusive) indication of safety and effectiveness, and either will not prescribe or are reluctant to prescribe absent such approval, manufacturers will seek to obtain FDA approval to make their products more appealing to that market. And, to the extent that the tort regime looks to FDA approval as the definition of the "standard of care," the call to get new uses on-label will come from sources other than the FDA.

Fourth, the court must again note that off-label prescriptions, presently legal, do constitute the most effective treatment available for some conditions. Through the government's well-intentioned efforts to prevent misleading information from being communicated, a great deal of truthful information will also be embargoed. In this case, the truthful information may be life saving information, or information than makes a life with a debilitating condition more comfortable.

Finally, this alternative comports with the Supreme Court's preference for combating potentially problematic speech with more speech. In choosing between the dissemination of more or less information "[i]t is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us." Virginia State Board of Pharmacy, 425 U.S. at 770 (quoted in 44 Liquormart, 517 U.S. at 497; Linmark Assoc., Inc. v. Willingboro, 431 U.S. 85, 97 (1977)).

## III. CONCLUSION

In sum, the court finds that the restrictions in the Guidance Documents are more extensive than necessary to serve the asserted government interest and that they unduly burden important speech. Therefore, the Guidance Docmuents fail the fourth prong of the Central Hudson test, rendering them incompatible with the First Amendment.

A separate order and injunction shall issue this day.

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Royce C. Lamberth
United States District Judge

DATE:

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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| WASHINGTON LEGAL FOUNDATION,<br><br>Plaintiff,<br><br>v.<br><br>MICHAEL A. FRIEDMAN, M.D., in his official capacity as Acting Commissioner, Food and Drug Administration and,<br><br>DONNA SHALALA, in her official capacity as Secretary, Department of Health and Human Services<br><br>Defendants. | ) | Civil Action No. 94-1306 (RCL) |

ORDER GRANTING SUMMARY
JUDGMENT AND PERMANENT INJUNCTION

This action is before the Court on the Cross-Motions for Summary Judgment filed by Plaintiff Washington Legal Foundation("WLF") and Defendants Michael A. Friedman and Donna Shalala.

Having reviewed the memoranda and other materials submitted, having heard oral argument and otherwise being fully advised:

THE COURT FINDS that there are no genuine issues of material fact and that WLF is entitled to judgment as a matter of law; accordingly,

THE COURT GRANTS WLF's Motion for Summary Judgment;

THE COURT DENIES Defendants' Cross-Motion Summary Judgment;

THE COURT FINDS AND DECLARES that the policies, rules and regulations of the United States Food and Drug Administration ("FDA") set forth in the Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data, 61 Fed. Reg. 52800 (Oct. 8, 1996) (the "Reprint Guidance"), Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52800 (Oct. 8, 1996)(the "Textbook Guidance"), and Final Guidance on Industry Supported Scientific and Educational Activities, 62 Fed. Reg. 64074 (Dec. 3, 1997)(the "Final CME Guidance") are contrary to rights secured by the United States Constitution and therefore must be set aside pursuant to 5 U.S.C. § 706(2)(B)except insofar as they are consistent with the injunctive provisions below.

THE COURT HEREBY ENJOINS Defendants, their successors, and all persons acting in concert with them or otherwise purporting to act on behalf of the United States (collectively "Defendants") from application or enforcement of any regulation, guidance, policy, order or other official action, as follows:

1. Defendants SHALL NOT in any way prohibit, restrict, sanction or otherwise seek to limit any pharmaceutical or medical device manufacturer or any other person:

a) from disseminating or redistributing to physicians or other medical professionals any article concerning prescription drugs or medical devices previously published in a bona fide peer-reviewed professional journal, regardless of whether such article includes a significant or exclusive focus on uses of drugs or medical devices other than those approved by FDA and regardless of whether such article reports the original study on which FDA approval of the drug or device in question was based;

b) from disseminating or redistributing to physicians or other medical professionals

any reference textbook (including any medical textbook or compendium) or any portion thereof published by a bona fide independent publisher and otherwise generally available for sale in bookstores or other distribution channels where similar books are normally available, regardless of whether such reference textbook or portion thereof includes a significant or exclusive focus on uses of drugs or medical devices other than those approved by FDA; or

c) from suggesting content or speakers to an independent program provider in connection with a continuing medical education seminar program or other symposium, regardless of whether uses of drugs and medical devices other than those approved by FDA are to be discussed.

2. For purposes of this injunction, a "bona fide peer-reviewed journal" is a journal that uses experts to objectively review and select, reject, or provide comments about proposed articles. Such experts should have demonstrated expertise in the subject of the article under review, and be independent from the journal.

3. For purposes of this injunction, a "bona fide independent publisher" is a publisher that has no common ownership or other corporate affiliation with a pharmaceutical or medical device manufacturer and whose principal business is the publication and distribution of books through normal distribution channels.

4. For purposes of this injunction, an "independent program provider" is an entity that has no common ownership or other corporate affiliation with a pharmaceutical or medical device manufacturer, that engages in the business of creating and producing continuing medical education seminars, program or other symposia and that is accredited by a national accrediting organization

pertinent to the topic of such seminars, programs or symposia.

5. Nothing herein shall be construed to limit Defendants' application or enforcement of any rules, regulations, guidances, statutes or other provisions of law that sanction the dissemination or redistribution of articles or reference textbooks or for seminars or symposia that include references to uses of drugs or medical devices other than those approved by FDA to disclose (i) its interest in such drugs or devices, and (ii) the fact that the use discussed has not been approved by FDA.

6. Defendants shall cause this injunction to be published in the Federal Register within 30 days of the date hereof.

IT IS SO ORDERED on this 30th day of July, 1998.

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THE HONORABLE ROYCE C. LAMBERTH
United States District Judge